REMARKS

Claims 33-34, 38-40, 87, 89, 92, 101, 103-107 and 109-122 are currently pending.

I. Obviousness-Type Double Patenting Rejection

A. U.S. Patent No. 7,169,766.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 15 and 16 of U.S. Patent No. 7,169,766 ("the '766 patent") in view of M. Arens, J. Clin. Virology, 22: 11-29 (2001) ("Arens"). Claim 15 of the '766 patent recites, *inter alia*, a method of treating a hepatitis C virus ("HCV") infection by administering a 2'-branched triazolopyridine, imidazolopyridine, or pyrazolopyrimidine nucleoside in combination with a second anti-HCV agent. Claim 16 of the '766 patent recites the method of claim 15, wherein the second anti-HCV agent is interferon.

An obviousness-type double patenting rejection is appropriate only when the claims at issue are not "patentably distinct" from the claims of a commonly owned earlier patent. *Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001). A claim is not patentably distinct from an earlier patent claim if the later claim is "obvious over, or anticipated by, the earlier claim." *Id.* at 968. Applicants request withdrawal of the double patenting rejection because the instant claims are not obvious over or anticipated by the claims of the '766 patent.

The instant claims recite, *inter alia*, methods of treating a HCV infection in a host using 2'-C-branched pyrimidine nucleosides, identifying viral resistance in the host, and administering a second anti-HCV agent. The anti-HCV compounds of the claims of the '766 patent are 2'-branched triazolopyridine, imidazolopyridine, or pyrazolopyrimidine nucleosides. In other words, the compounds of the claims of '766 patent are not the same, and do not overlap with, the compounds of the instant claims. Furthermore, the claims of the '766 patent do not teach or suggest the identification of viral resistance prior to the selection and administration of a second anti-HCV agent. Thus, the instant claims are not obvious over, and are therefore patentably distinct from the claims of '766 patent.

Moreover, the policy behind a double patenting rejection—the prevention of an unjustified extension of the term of a patent—does not support the Examiner's rejection in this case. *See In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986) ("the basis for... obviousness-type

double patenting rejections is timewise extension of the patent right"). Allowance of the instant claims, directed to combination therapy with a 2'-C-branched pyrimidine nucleoside and a second drug, including the intermediate step of identifying viral resistance to the 2'-C-substituted pyrimidine nucleoside, would not result in the extension of the term of the '766 patent, which claims only combination therapy with 2'-C-branched triazolopyridine, imidazolopyridine, or pyrazolopyrimidine nucleosides without mention of the identification of viral resistance. Simply put, the '766 patent does not protect the same invention of the instant claims, therefore, Applicants respectfully request that the double patenting rejection be withdrawn.

The Office Action alleges that Arens cures the defect of the '766 patent because Arens teaches that HCV can be treated with a combination of antiviral drugs, and that genotyping of the virus "is important to the therapeutic regimen." (Office Action, page 4). Arens teaches the use of ribavirin and interferon alpha-2b in combination to treat HCV infections. (Arens, page 18). Arens also teaches that genotyping used in connection with the above treatment was used to identify factors associated with a favorable viral response. (*Id.*). Arens does not teach or suggest the identification of HCV resistance to 2'-C-branched nucleosides. Arens does not teach or suggest the combination of the claimed 2'-C-branched pyrimidine nucleosides with drugs that induce a mutation in the virus at a location other than an amino acid mutation in the highly conserved sequence recited in claim 33. Furthermore, Arens does not teach or suggest that genotyping would be useful in the specific combination therapy of claim 33. Thus, one of ordinary skill in the art would have had no motivation to combine the teachings of Arens with claims 15 and 16 of the '766 patent.

Moreover, Arens does not provide any information about the specific mutations of the instant claims. The Office Action points to a number of teachings in Arens regarding the identification of viral resistance in hepatitis B virus and cytomegalovirus infections, but does not demonstrate the same for HCV. (Office Action, page 4). Instead, the Office Action states that the teachings of Arens regarding hepatitis B virus and cytomegalovirus can be broadly applied "[a]s a general genotyping approach for all of the viruses," including HCV. (*Id.*). Applicants respectfully disagree. Arens does not teach a general genotyping approach to all the viruses discussed therein. To the contrary, Arens provides a separate, distinct discussion of each virus with details about the unique mutations of each virus and resistance to specific drugs used to treat each specific viral infection. For example, one of the selections from Arens cited in the

Office Action is a discussion of mutations and drug resistance specific to cytomegalovirus at page 20. (*Id.*). In this section of the article, Arens teaches that ganciclovir, foscarnet and cidofovir are approved drugs for treating cytomegalovirus, each of which may provoke resistance through specific mutations in the UL97 and/or UL54 genes of cytomegalovirus. (Arens, pages 20-21). One of ordinary skill in the art would not expect that this specific teaching regarding cytomegalovirus would have any use in the treatment of HCV, not to mention the specific combination therapy provided in claim 33. In Arens's discussion about HCV, 2'-C-branched nucleosides are not discussed.

Furthermore, Arens teaches that, with respect to genotyping techniques, the location of the mutations that confer viral resistance must be known in order to evaluate viral resistance. (*Id.*). Therefore, one of ordinary skill in the art, at the time of the invention, would have had to have known specific resistance-conferring mutations in the HCV genome in order to evaluate drug resistance in HCV. And, with respect to HCV, such teachings are absent in the art cited by the Examiner. Indeed, Arens teaches away from the instant claims because it teaches that viral resistance cannot be evaluated absent knowledge of the location of a specific HCV mutation. *See Peterson,* 315 F.3d at 1331 (applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect).

Furthermore, Arens itself admits to the difficulty in identifying accurate genotype data for HCV. (Arens, page 20). The Examiner has not provided any teaching of these specific HCV mutations. To the extent that the Examiner points to the teaching of genotyping methods in Arens, such teachings are in general terms or are specific to cytomegalovirus or HBV— not HCV nor the mutations relevant to the compounds of claim 33. (Office Action, page 4, Arens, page 13).

In sum, the Office Action does not provide sufficient evidence to support the allegation that one of ordinary skill in the art would have been motivated to practice the method of claim 33 solely based on claims 15 and 16 of the '766 patent in view of Arens. Thus, the instant claims are not obvious over, and therefore patentably distinct from, the claims of the '766 patent in view of Arens. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

B. U.S. Patent No. 7,192,936.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable

over claims 2-7, 9, 12-13 and 17 of U.S. Patent No. 7,192,936 ("the '936 patent") in view of Arens. Claim 2 of the '936 patent recites a method of treating a host infected with a *Flaviviridae* virus with 2'-C-trifluoromethyl substituted pyrimidine nucleosides. Claim 3 of the '936 patent recites the method of claim 2, wherein the virus is HCV, and claims 4-7 of the '936 patent further recite the above methods in combination with a second antiviral agent. Claims 9, 12-13 and 17 of the '936 patent recite enantiomeric purities and dosage forms of the compounds of claim 2. As is the case with the claims of the '766 patent, the claims of the '936 patent do not teach or suggest the identification of viral resistance prior to the selection and administration of a second anti-HCV agent. Thus, the instant claims are directed to an entirely different invention than the claims of the '936 patent.

Arens does not cure this defect. As discussed above, the teachings of Arens are not specific to the treatment of HCV with the combination therapy recited in claim 33, nor are they specific to the mutations relevant to the method of claim 33. (Arens, page 13). For the reasons discussed above, one of ordinary skill in the art would not be motivated, based on the claims of the '936 patent, to apply the teachings of Arens to arrive at the method of claim 33. Therefore, the Office Action has not provided evidence to support an obviousness-type double patenting rejection of claim 33 over the claims of the '936 patent in view of Arens. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 103

A. The instant claims are not obvious over Carroll in view of Arens.

Claims 33, 34, 92, 104, 107 and 109-122 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carroll in view of Arens, *J. Clin. Virology*, 22: 11-29 (2001) ("Arens"). (Office Action, page 8). Specifically, the Office Action alleges that the claims are obvious because Carroll teaches 2'-branched ribonucleosides in combination with second antiviral agents and Arens teaches genotyping as a part of HCV therapy. (Office Action, pages 9-10). Applicants respectfully disagree.

Claim 33 recites, *inter alia*, a method of treating a hepatitis C virus infection in a host comprising (a) administering a 2'-branched nucleoside, (b) identifying viral resistance to the 2'-branched nucleoside, and (c) administering one or more additional drugs that induce a mutation in the virus at a location other than a mutation of a nucleotide that results in a change from serine

to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Rejected claims 39-40, 89, 101, 103, 105 and 106 depend from claim 33.

Neither Carroll nor Arens teaches or suggests methods of treating resistant strains of HCV with the 2'-C-branched nucleosides of clam 33. Carroll teaches a broad selection of antiviral compounds, including certain 2'-C-branched nucleosides. Carroll teaches combination therapy generally, including the use of interferon, but Carroll is silent as to the step of identifying viral resistance. The Office Action alleges that Arens cures this defect because it teaches genotyping viruses in a treatment regimen, including HCV. (Office Action, page 9).

Arens does not cure the defects of Carroll because Arens teaches only the general use of genotyping in connection with HCV therapy. (*Id.*). Arens does not teach the identification of HCV resistance to 2'-C-branched nucleosides. Arens does not teach the combination of 2'-C-branched nucleosides with drugs that induce a mutation in the virus at a location other than an amino acid mutation in the highly conserved sequence recited in claim 33. Furthermore, Arens does not teach that genotyping would be useful in the specific combination therapy of claim 33. Moreover, as discussed above, Arens admits to the difficulty in identifying accurate genotype data for HCV. (Arens, page 20).

The Office Action points to a number of teachings in Arens regarding identifying resistance in hepatitis B virus and cytomegalovirus, but does not identify the same regarding HCV. (Office Action, pages 9-10). Instead, the Office Action states that the teachings of Arens regarding hepatitis B virus and cytomegalovirus can be broadly applied "[a]s a general genotyping approach for all of the viruses," including HCV. (Office Action, page 10). Applicants respectfully disagree. Arens does not teach a general genotyping approach to all the viruses discussed therein. To the contrary, Arens provides a separate discussion of each individual virus that includes details about the unique mutations of each virus and resistance to specific drugs used to treat the specific viral infection. For example, an excerpt from Arens cited in the Office Action is a discussion of mutations and drug resistance specific to cytomegalovirus. (Arens, page 20). In this section of the article, Arens teaches that gangicyclovir, foscarnet and cidofovir are approved drugs for treating cytomegalovirus, each of which may provoke resistance through specific mutations in the UL97 and/or UL54 genes of the cytomegalovirus viron. (Arens, pages 20-21). One of ordinary skill in the art would not expect that this specific

teaching regarding cytomegalovirus would have any use in the treatment of HCV, not to mention the specific combination therapy provided in claim 33.

Furthermore, Arens teaches that, with respect to genotyping techniques, the location of the mutations that confer viral resistance must be known in order to evaluate viral resistance. (Arens, page 20). Therefore, one of ordinary skill in the art at the time of the invention would have had to have known specific resistance-conferring mutations in the HCV genome in order to evaluate drug resistance in HCV. As mentioned above, because the Office has not provided any teaching of these specific HCV mutations, one of ordinary skill in the art is left with little guidance as to how to practice the method of claim 33 based on Carroll and Arens alone. Further, as mentioned above, Arens teaches away from the instant claims because it teaches that viral resistance cannot be evaluated absent knowledge of the location of a specific HCV mutation. *See Peterson,* 315 F.3d at 1331 (applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect).

Therefore, based on the teachings of Carroll and Arens, one of ordinary skill in the art would have had no motivation to select a 2'-C-branched nucleoside of the instant claims, identify viral resistance in a HCV-infected host, and further administer a drug which induces a mutation in the virus at a location other than an amino acid mutation in the highly conserved consensus sequence recited in claim 33. Arens' general teaching of genotyping does not provide any insight into any of these specific elements of the combination therapy of claim 33, and one of ordinary skill in the art would have had no motivation to try the claimed combination therapy, nor would there be a reasonable expectation that the specific combination would succeed in treating HCV. *See KSR International Co. v. Teleflex Inc.*, 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385, 1395 (2007) (Examiner must "identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does."); *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (reasonable expectation of success). For these reasons, claim 33 is not obvious over Carroll in view of Arens. Because claims 34, 92, 104, 107 and 109-122 each depend from claim 33, they are also not obvious over Carroll in view of Arens. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

B. The instant claims are not obvious over Carroll in view of Arens and Sinko.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carroll in view of Arens, further in view of Sinko *et al.* (Office Action, pages 10-11). The Office Action alleges that because Carroll teaches 2'-branched nucleosides in combination with second antiviral agents, Arens teaches genotyping of HCV, and Sinko teaches that the use of a valine ester increases the bioavailability of acyclovir, the instant claims are obvious. (*Id.*). Applicants respectfully disagree.

Carroll in view of Arens is discussed above. Sinko does not cure the defects of Carroll and Arens because Sinko merely teaches that the valine ester of acyclovir has improved oral bioavailability. Because Sinko is silent as to the genus of compounds of claim 33, viral resistance, and methods of treating resistant strains of hepatitis C virus, one of ordinary skill in the art would have no reason to combine the teachings of Carroll, Arens and Sinko to arrive at instant claim 33. *See KSR*, 82 U.S.P.Q.2d at 1395 (Examiner must "identify a reason that would have prompted a person of ordinary skill…to combine the elements in the way the claimed new invention does."). Thus, claim 33 is not obvious over Carroll in view of Arens and Sinko. Because claims 34, 39-40, 89, 92, 101, 103-107 and 109-122 each depend from claim 33, they are also not obvious over Carroll in view of Arens and Sinko. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The fee for a one-month extension of time is provided herewith. The Commissioner is hereby authorized to charge any other required fees, or any credits, to Jones Day deposit account no. 50-3013 (referencing 417451-999064).

If the Examiner believes it would be useful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 314-1200.

Respectfully submitted,

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